

REMARKS

With entry of the instant amendment, claims 1-4, 7-11, 13, 14, 16, 17, 22-26, 29-32, and 50-56 are currently pending.

Claim 50 has been amended to recite a V_H with a cysteine at amino acid position 44, which heavy chain comprises the CDRs of SEQ ID NO:2 and is at least 90% identical to SEQ ID NO:2; and a V_L with a cysteine at amino acid position 100, which light chain comprises the CDRs of SEQ ID NO:4 and is at least 90% identical to SEQ ID NO:4. This amendment adds no new matter. Support for "at least 90% identity" can be found, *e.g.*, on page 12, lines 19-22. Support for the additional amendments to claim 50 can be found, *e.g.*, on page 21, lines 3-5, which teaches that the definition of specificity applies to CDRs; on page 19, line 32 through page 20, line, which teaches that the V_H and V_L structures are known in the art (citing Kabat and Wu, which is incorporated by reference) and that the positions of the V_H and V_L are with reference to Kabat and Wu; and in Figure 1, which provide the heavy and light chain variable region sequences.

New claim 56 adds no new matter and reflects claim 50 prior to amendment.

Rejection under 35 U.S.C. § 103

Claims 1-4, 7-11, 13, 14, 16, 17, 22-26, 29-32, and 50-55 stand rejected as allegedly obvious over Ghetie *et al.* in view of the additional references cited in section 6 of the Office Action of May 23, 2005. The Examiner contends that while it may be unobvious to obtain "just any" DNA from a particular cell, obtaining the V_H and V_L sequences of a monoclonal antibody produced by a hybridoma is routinely performed. Further, the Examiner argues that it is reasonable to conclude that the hybridoma taught by Shen *et al.* is the same as the hybridoma in the instant application because Mansfield *et al.* (*Blood* 90:2020-2026, 1997), which the Examiner characterizes as the inventor's own work describing the invention, states that the REB4 hybridoma was from the Royal Free Hospital in London (which was the institutional affiliation of two of the authors of Shen *et al.*). Applicants have traversed the rejection for reasons of record.

First, as previously explained, the law is clear: knowledge of general methods, in this case sequencing V_H and V_L regions of antibodies, does not render any particular sequence obvious. Although *In re Deuel* relates to a nucleic acid sequence, the holdings are applicable here, as the claims require recombinant RFB4 proteins having particular modifications. The claims rely on particular nucleic acid sequences, *i.e.*, the nucleic acids encoding SEQ ID NO:2 and SEQ ID NO:4.

Further, the Examiner's position that the RFB4 hybridoma taught by Shen *et al.* can reasonably be assumed to be the same as the hybridoma in the instant application does not necessarily lead to the precise sequences taught and claimed in the instant application. The designation "RFB4" by Shen *et al.* provides no structural information regarding the identity of the antibody. Even if one of skill assumes that the hybridoma was the same as that used here, one of skill would not be able to make the claimed sequences based on the combination of references cited by the Examiner.

Next, with regard to the FitzGerald declaration filed March 11, 2004, the Examiner alleges that one of skill would expect the RFB4-toxin conjugates to have increased production, better toxicity, and retention of affinity based on the cited art. However, Dr. FitzGerald attests to the fact that the finding that RFB4 immunotoxins retain the binding specificity and affinity of the parent RFB4 IgG is unusual. The Examiner cites Reiter *et al.* (*Biochemistry*) as showing better cytotoxicity of a dsFv compared to an scFv, and as teaching that an scFv can retain the specificity and affinity of IgG (emphasis added). However, there is no reasoning or evidence provided in the rejection as to why one of skill would conclude that the RFB4 antibody-toxin conjugates claimed here would in fact have these properties. The mere teaching that a composition could possibly have a characteristic does not lead to the logical conclusion that all of such compositions would have that characteristic. Indeed, Dr. FitzGerald explains that typically binding affinity is lowered in such a conjugate in comparison to the parent antibody.

In addition, Dr. FitzGerald explains that the superior toxicity and efficacy of RFB4ds(Fv)-PE38 not only in animal models, but also in human Phase I trials (referring to his previous Rule 1.132 Declaration, signed May 15, 2001, which is of record in this application)

was surprising and could not be predicted from the art (sections 9 and 10) of the March 11, 2004 FitzGerald Declaration. Indeed, the clinical trials referred to by Dr. FitzGerald showed that 11 patients achieved complete remission and 2 patient achieved partial remission when RFB4ds(Fv)-PE28 was administered to them (section 10 of the FitzGerald Declaration signed May 15, 2001). Again, the Examiner provides no evidence or reasoning as to why one of skill could predict such superior properties based on the cited art.

In summary, the rejection does not provide a proper case of *prima facie* obviousness. Further, even assuming *arguendo* that the claims could be considered *prima facie* obvious, the compositions have surprising and superior properties that were not predictable. In view of the foregoing, the claims are patentable over the art. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 50-55 were rejected as allegedly not enabled for sequences that have the specified cysteine substitutions in RFB4 sequences that have at least 95% identity to SEQ ID NO:2 or 4. The Examiner contends that the claims would encompass sequences that have changes in the CDRs and that it would be unpredictable as to which changes in the CDRs would provide an antibody having the binding affinity and specificity set forth in the claims. Although Applicants disagree, in order to expedite prosecution, claim 50 has been amended to recite that the sequences have the CDRs of SEQ ID NOs:2 and 4. Applicants believe that this amendment obviates the rejection applied to these claims.

With regard to new claim 56, which is the same as unamended claim 50, Applicants respectfully traverse. The claims relate to sequences having at least 95% identity to the reference sequences and defined functional characteristics. The Examiner argues that it would require undue experimentation to determine sequences within the scope of this claim. The question here is whether one of skill could without undue experimentation determine which embodiments would be operative or inoperative with expenditure of no more effort that is normally required in the art. As the Examiner acknowledges, the structures of V_H and V_L regions (*i.e.*, identification of framework regions and CDRs) are well known. Thus, one of skill

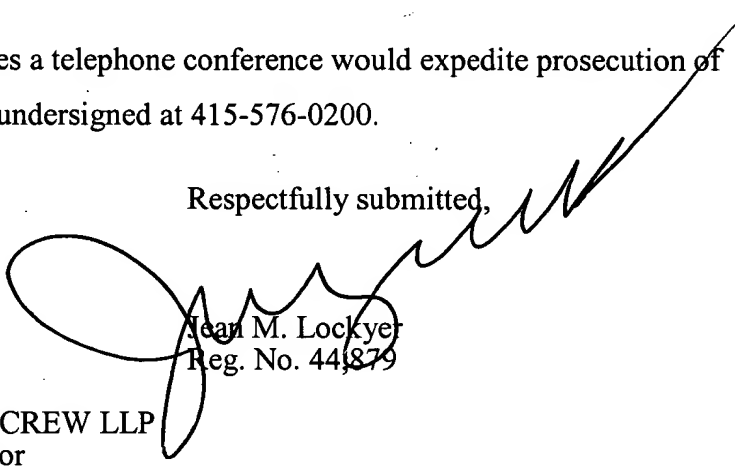
could logically use this knowledge to generate sequences that are operative, *i.e.*, that have the claimed functional limitations, without undue experimentation. In view of the foregoing, Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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